

Designing a high affinity ligand for the A₁ Adenosine Receptor

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ACMDD



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Adenosine Receptors (ARs)

A₁

A_{2A}

A_{2B}

A₃



A₁AR Activation¹:

- ↓ Heart rate & atrial contractility
- Anti-nociception
- Control of lipolysis

A₁AR Inhibition¹:

- Enhanced cognition
- Diuretic effects
- Inhibition of seizure activity

ischemic heart disease, anxiety, dementia, epilepsy, renal failure, diabetes

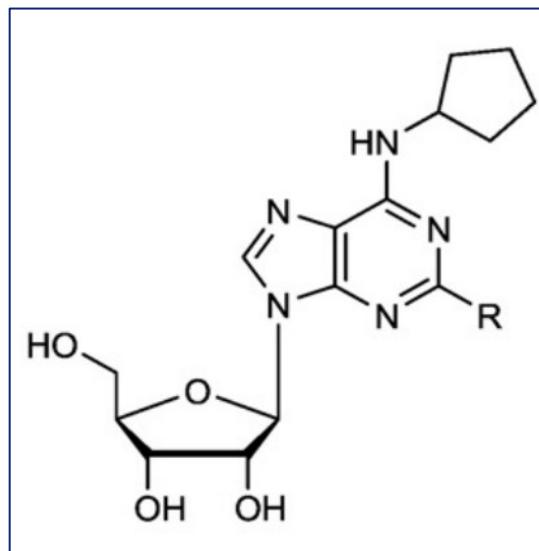


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A₁AR Ligands

- There are very few A₁AR drug candidates that have successfully progressed through clinical trials²



<https://doi.org/10.1016/j.bbamem.2010.12.017>

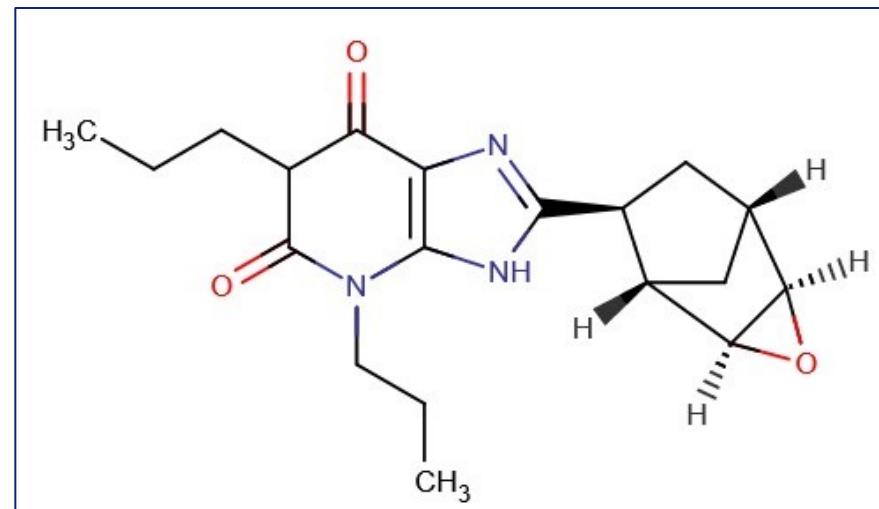
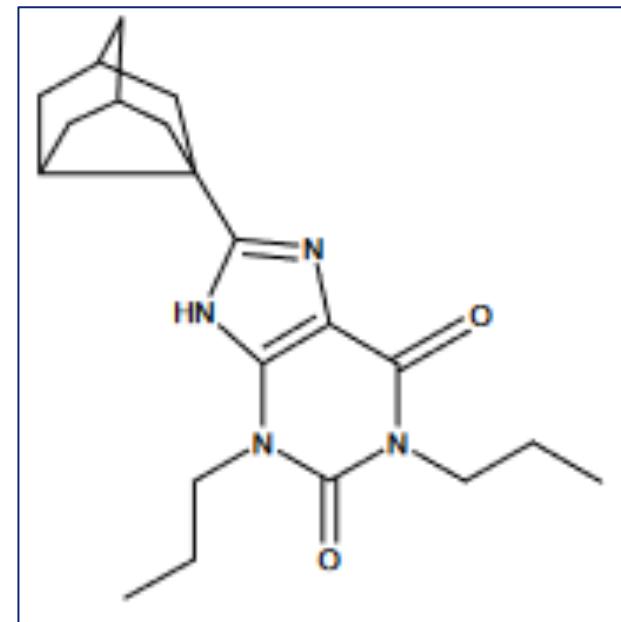


image: <https://go.drugbank.com/structures/DB06471/image.svg>



<https://doi.org/10.2217/14796678.4.2.117>

N6-cyclopentyl-adenosine
(CPA)



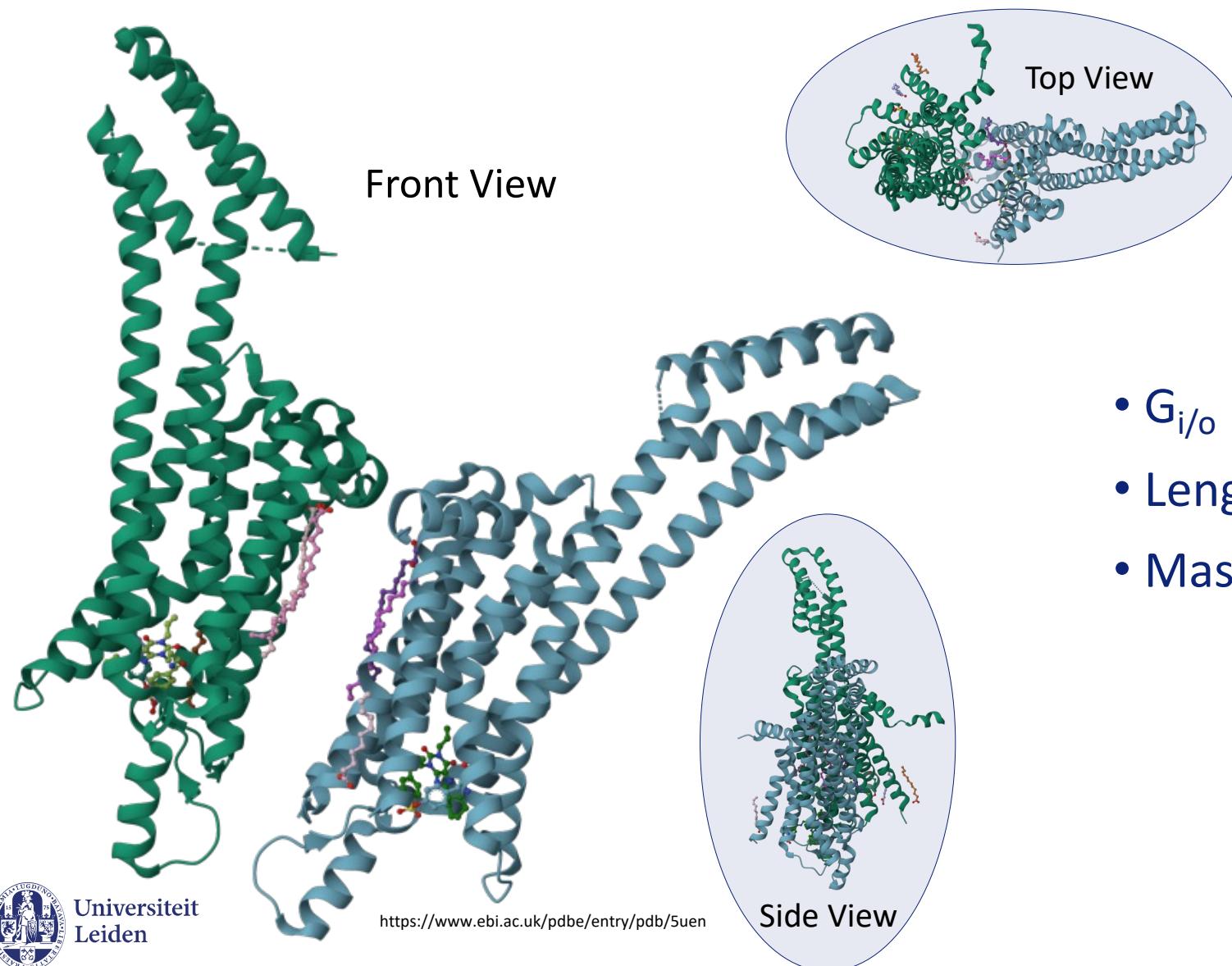
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Naxifylline

Rolofylline

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The A₁AR Structure



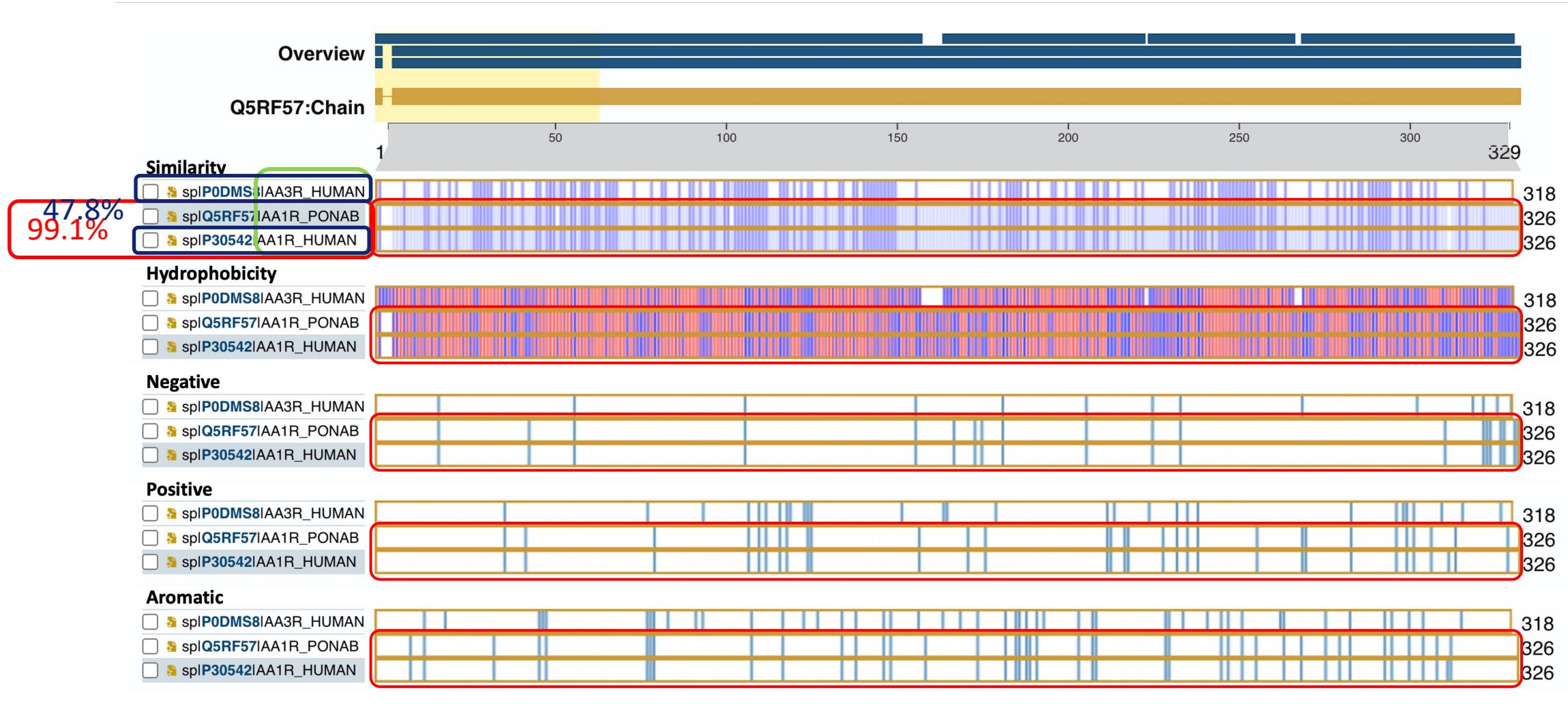
- G_{i/o} coupled³
- Length: 326 amino acids
- Mass: 36.5 kDa



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Comparison of A₁AR with similar proteins

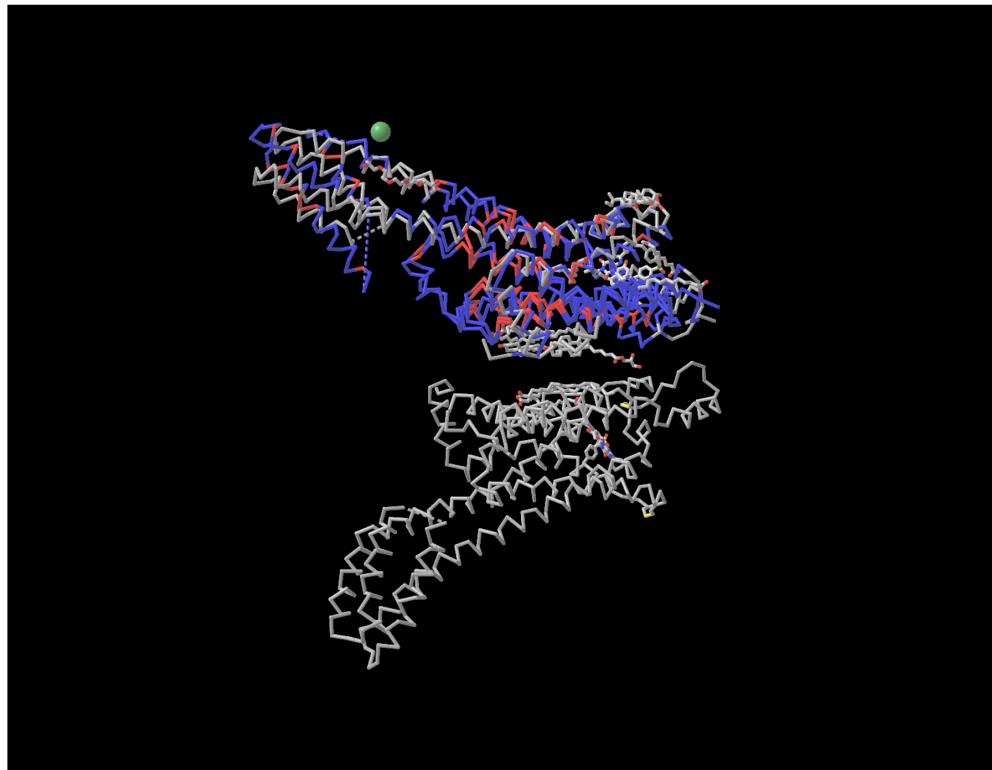


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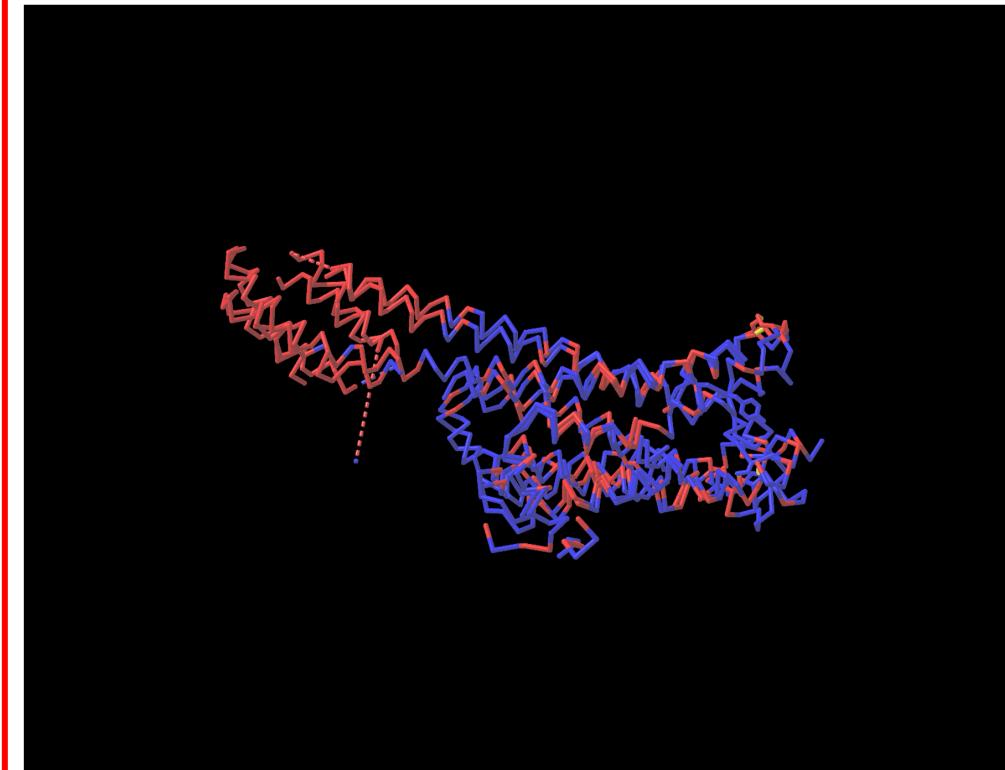
7WC4: Similar protein based on structure

5UEN & 7WC4 alignment



Realignment RMSD: 2.916 Å

5UEN & 7WC4 by sequence alignment



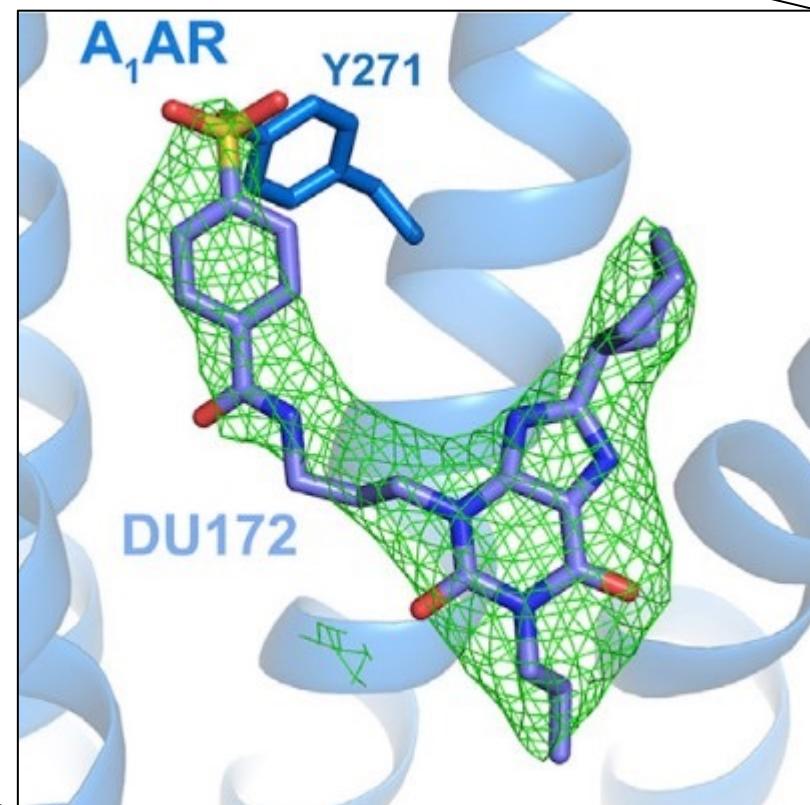
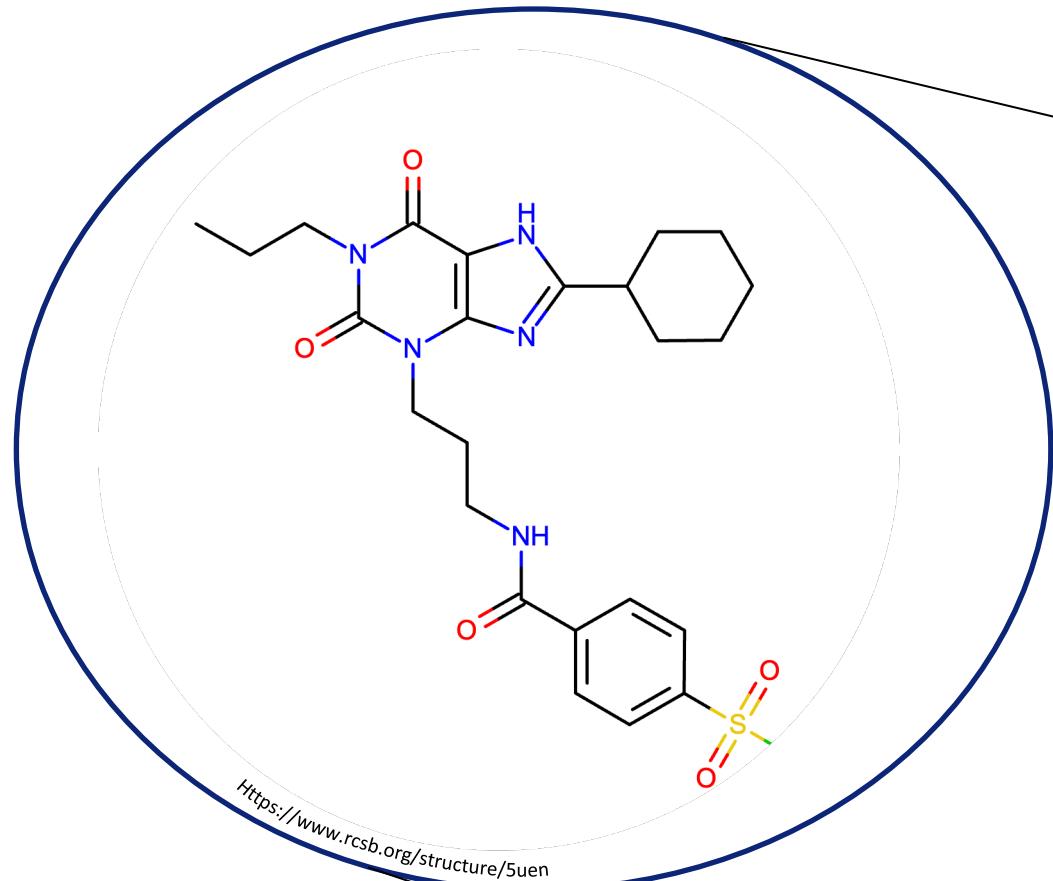
Realignment RMSD: 4.576 Å



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A₁AR Ligand: DU172

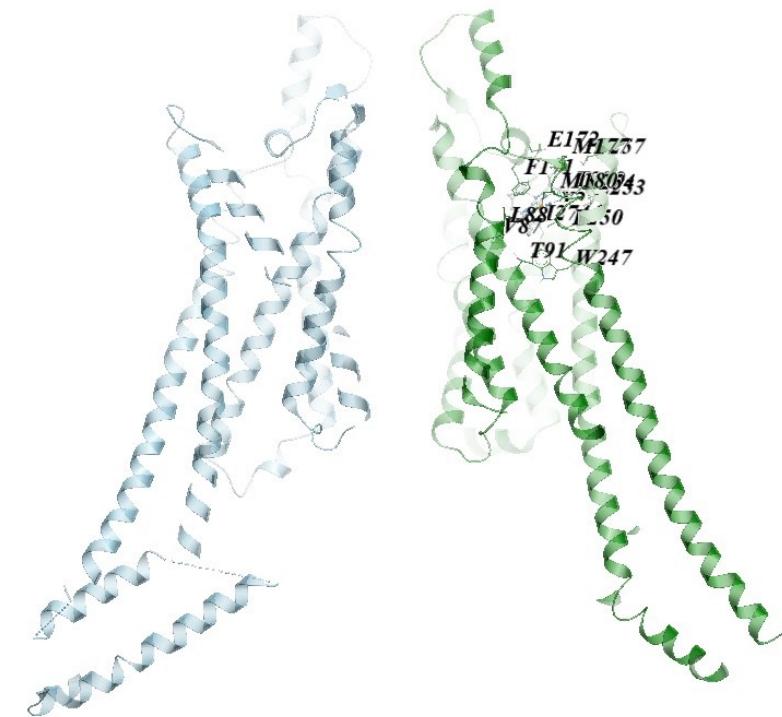
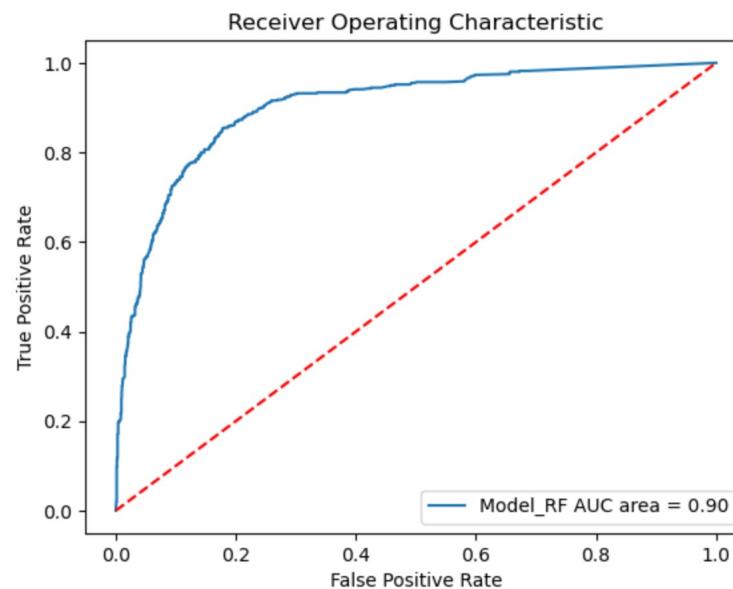
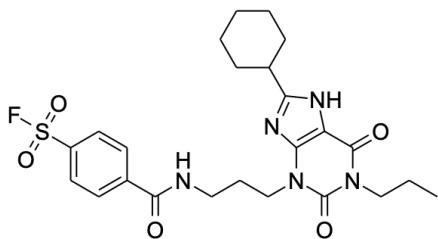


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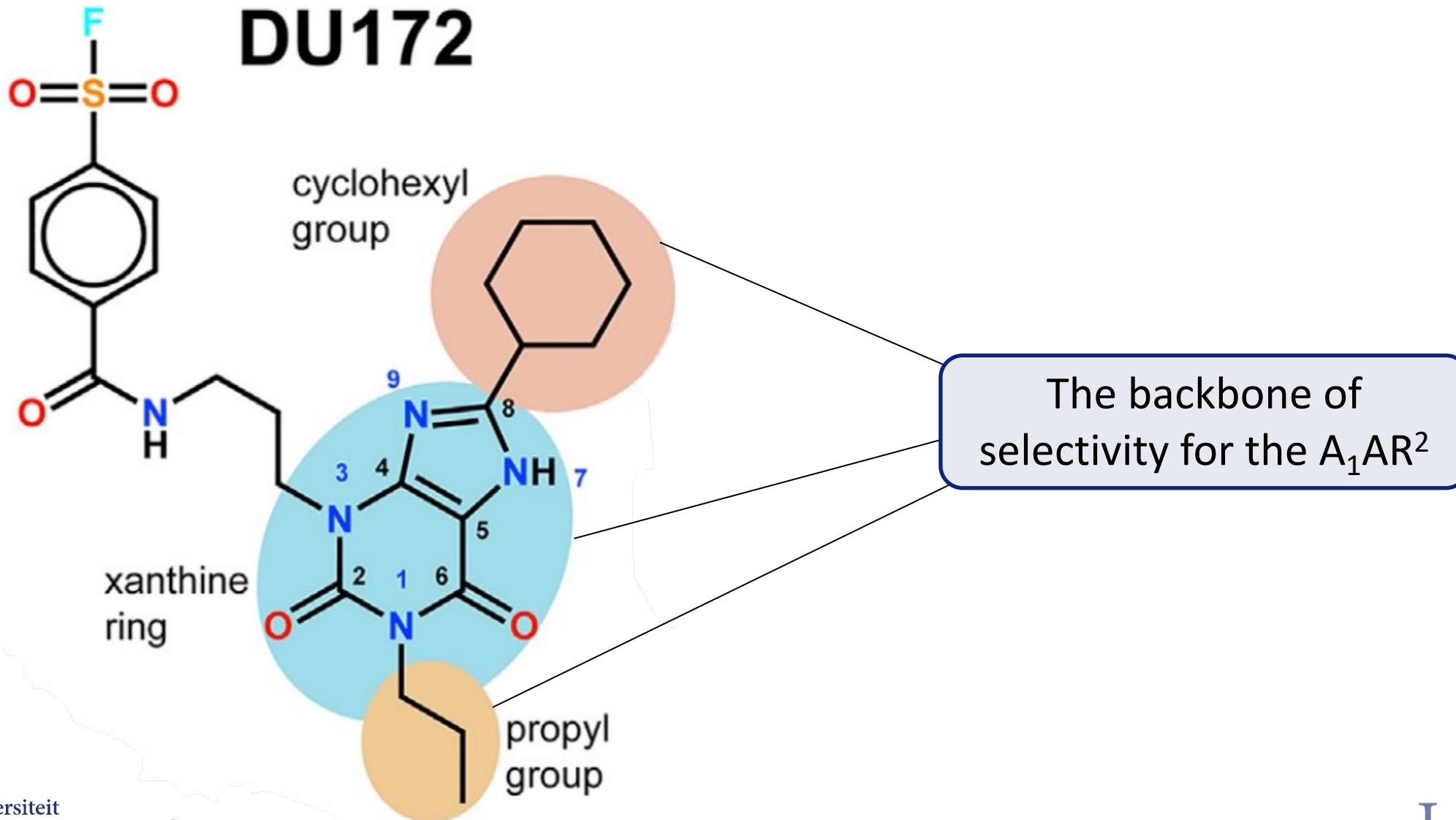
Predicting DU1 affinity to A₁AR

- Aim: Predict affinity score using machine learning and molecular docking.
- Target: A₁AR (ChEMBL226)
- Ligand: DU1 (ChEMBL144360)
- Redocking DU-1 by ICM-Pro



	SMILES	pChEMBL (ML)	pChEMBL (dock)	Average score	Affinity by ICM-pro
Ligand_00	<chem>CCN1C(=O)C2=C(N=C(N2)C3CCCC3)N(C1=O)CCCNC(=O)C4=CC=C(C=C4)S(=O)(=O)F</chem>	7.34	6.71	7.02	-28.15

Designing a Ligand with high affinity for A₁AR



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Predicting the affinity to A₁AR

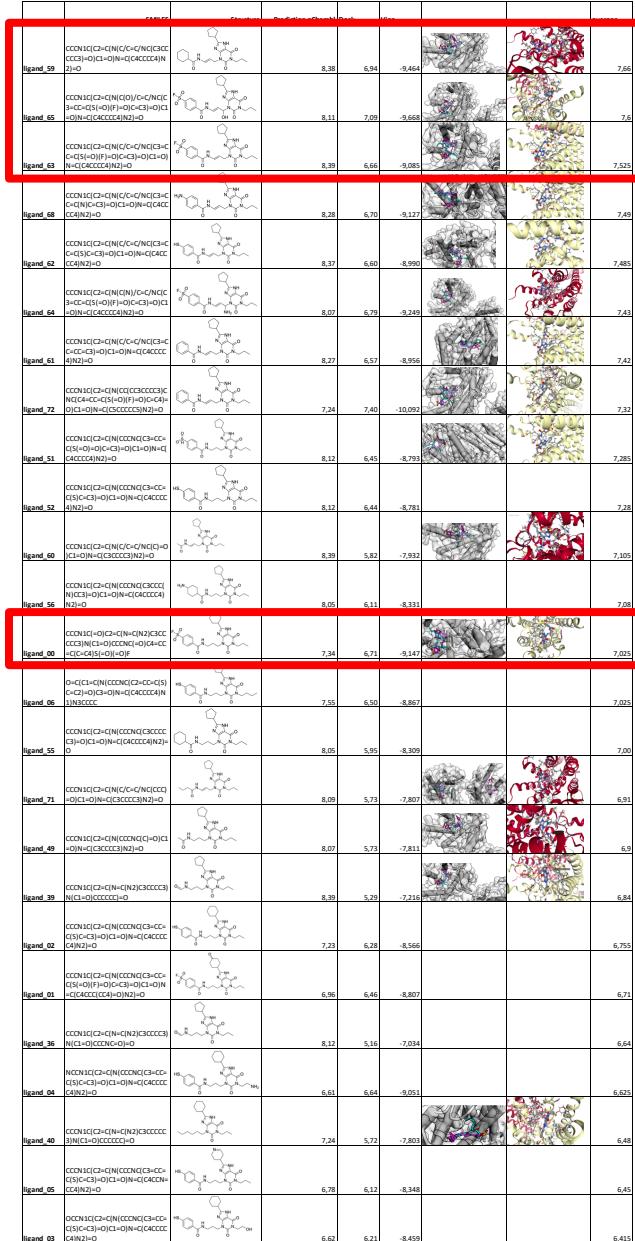
1. Design new ligands using DU1-scaffold
2. Predict affinity to A₁AR using machine learning
 1. If pChEMBL > 8.00 → molecular docking
3. Predict affinity to A₁AR using AutoDock Vina
4. Average

70 ligands



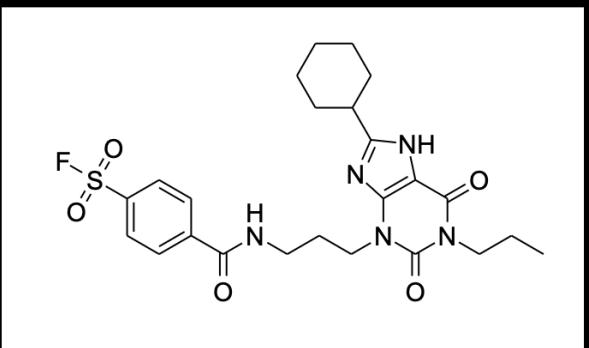
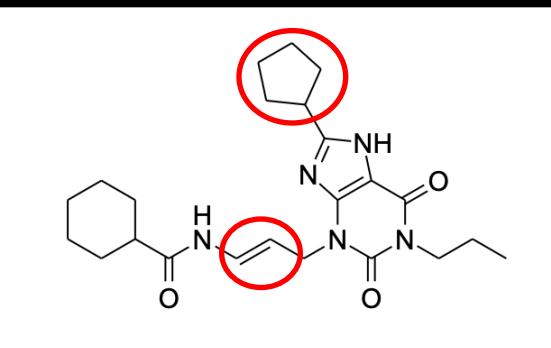
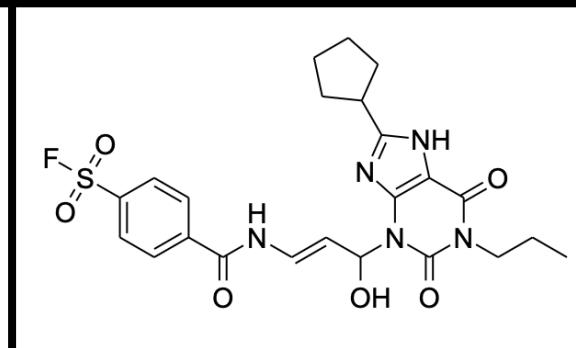
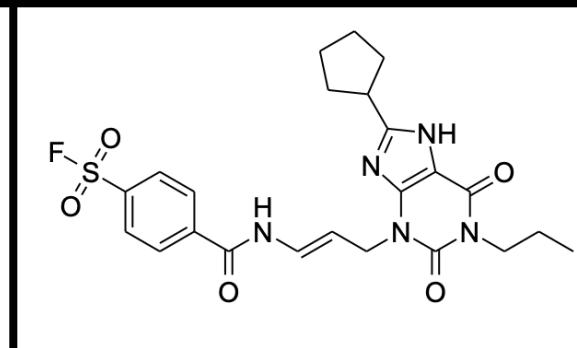
15 ligands

	SMILES	pChEMBL (ML)	pChEMBL (dock)	Average score
00	CCCN1C(=O)C2=C(N=C(N2)C3CCCCC3)N(C1=O)CC CNC(=O)C4=CC=C(C=C4)S(=O)(=O)F	7.34	6.71	7.02
59	CCCN1C(C2=C(N(C/C=C/NC(C3CCCCC3)=O)C1=O) N=C(C4CCCC4)N2)=O	8.38	6.94	7.66
65	CCCN1C(C2=C(N(C(O)/C=C/NC(C3=CC=C(S(=O)(F)=O)C=C3)=O)C1=O)N=C(C4CCCC4)N2)=O	8.11	7.09	7.60
63	CCCN1C(C2=C(N(C/C=C/NC(C3=CC=C(S(=O)(F)=O)C=C3)=O)C1=O)N=C(C4CCCC4)N2)=O	8.39	6.66	7.53

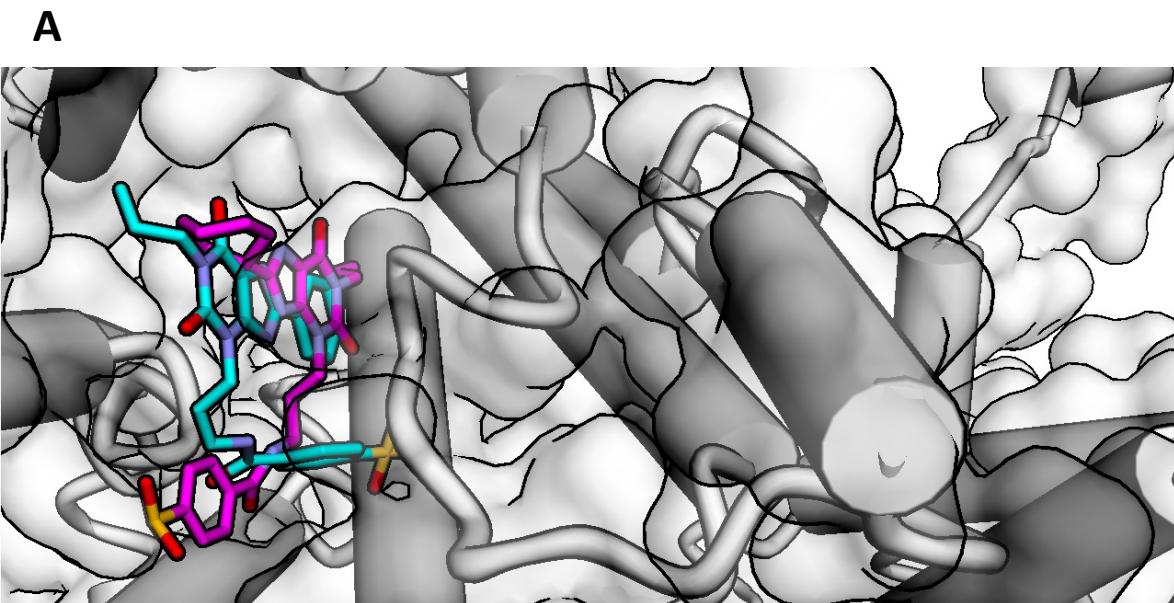


Overview A₁AR ligands

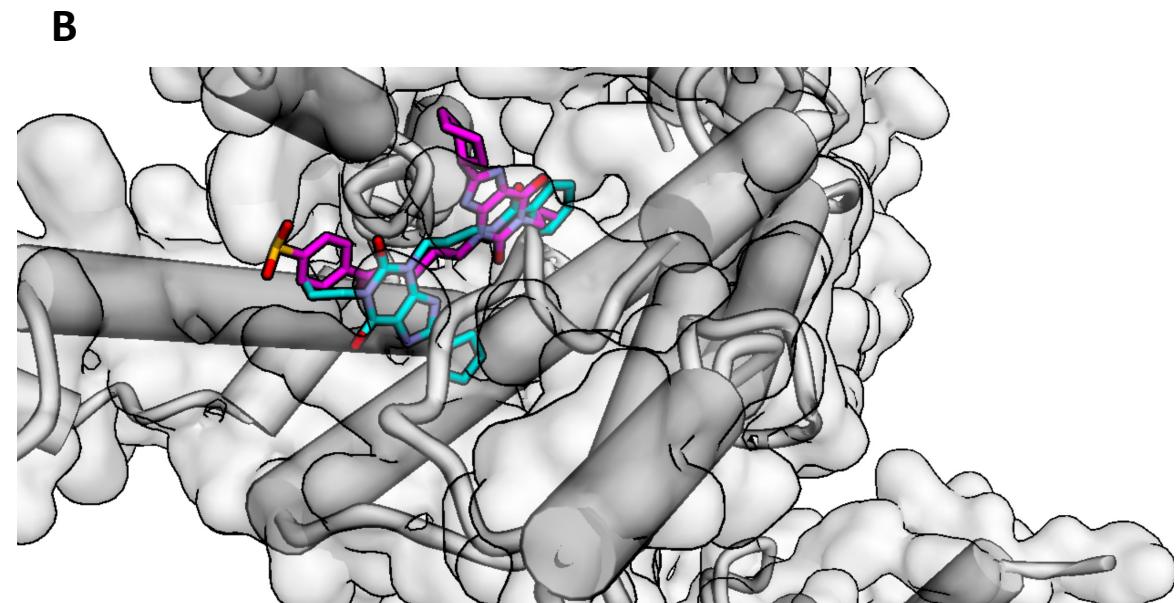
- Most important modifications

			
Ligand_00 (DU1)	Ligand_59	Ligand_65	Ligand_63
7.02	7.66	7.60	7.53

Docking of DU1 and ligand_59



DU1 (Ligand_00)



Ligand_59



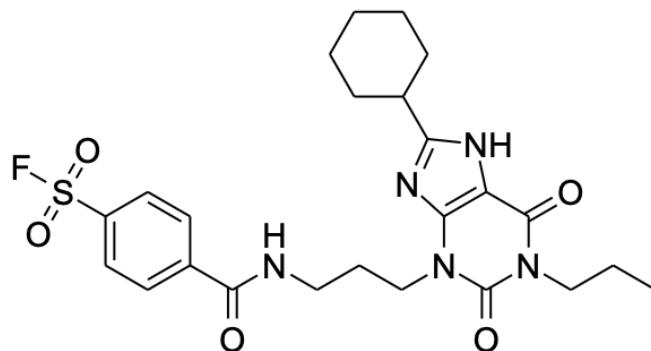
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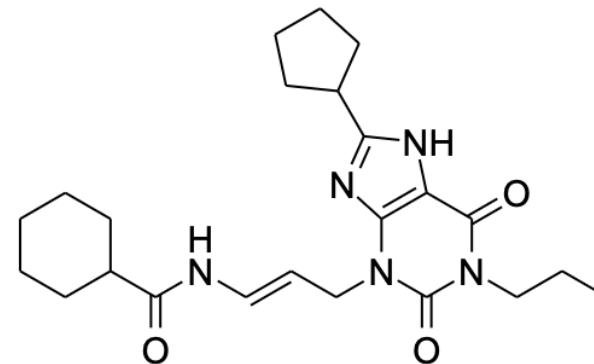
Summary

- DU1 was redocked in different docking software + machine learning
- A novel ligand with higher affinity for A₁AR was docked

DU1

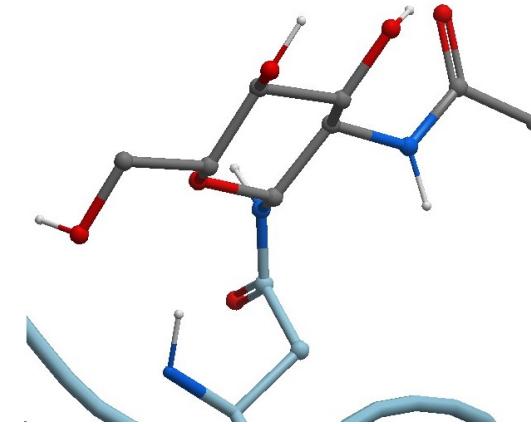


Ligand_59



Discussion and Future Perspectives

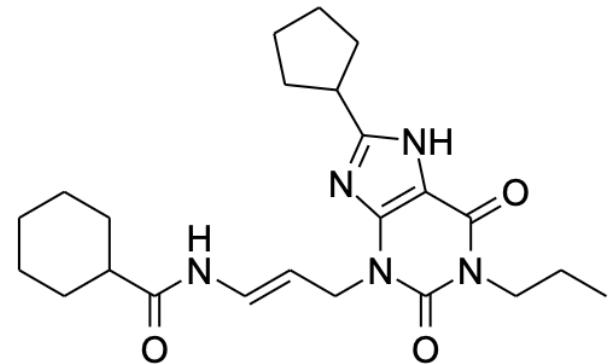
- Difference in docking scores
- Validation of docking scores is needed
- Three N-glycosylation sites
- Docking on the glycosylated A₁ AR



Thank you for listening, questions? 😊



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